FORM PTO-1390 (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEYS DOCKET NUMBER: 742439-3

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/926807

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	
PCT/IB00/00837	22 June 2000	24 June 1999

TITLE OF INVENTION: NAPHTHOQUINONE DERIVATIVES AND THEIR USE IN THE TREATMENT AND CONTROL OF TUBERCULOSIS

APPLICANT(S) FOR DO/EO/US: Jacobus Johannes Marion MEYER and Namrita LALL

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☒ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information: Application Data Sheet

JC07 Rec'd PCT/PTO 21 DEC 2001

U.S. APPLICATION NO (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEYS DOCKET NUMBER
09/926807	PCT/IB00/00837	742439-3

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1) – (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	890.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(3)) paid to USPTO **$740.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$0	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	13- 20 =	0	X **$18.00**	$0	
Independent claims	2- 3 =	0	X **$84.00**	$0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$280.00	
TOTAL OF ABOVE CALCULATIONS =				$1170.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$0	
SUBTOTAL =				$1170.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$0	
TOTAL NATIONAL FEE =				$1170.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$0	
TOTAL FEES ENCLOSED =				$1170.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $1170.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-2380 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☐ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2380. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Jason H. Vick
NAME

45,285
REGISTRATION NUMBER

09/926807
PCT/IB00/00837
JC07 Rec'd PCT/PTO 21 DEC 2001

NAPHTHOQUINONE DERIVATIVES AND THEIR USE IN THE TREATMENT AND CONTROL OF TUBERCULOSIS

BACKGROUND OF THE INVENTION

THIS invention relates to the treatment and control of tuberculosis caused by *Mycobacterium tuberculosis* and in particular to the use of naphthoquinone derivatives in such treatment and control.

Tuberculosis (TB) remains a serious health problem in many regions of the world, especially in developing nations. It is a contagious disease and is becoming epidemic in some parts of the world. It is estimated that 30-60% of adults in developing countries are infected with *Mycobacterium tuberculosis*. Approximately 8-10 million individuals develop clinical TB and 3 million die of TB each year (WHO/IUATLD, 1989).

In South Africa, over 3 in every thousand people die of TB, the highest rate in the world, while one out of every 200 people suffers from active tuberculosis. Tuberculosis is the most commonly notified disease in South Africa and the fifth largest cause of death among the black population (South African Tuberculosis Association, 1998).

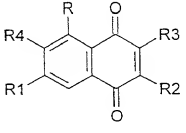
In the United States, the number of TB cases steadily decreased until 1986 when an increase was noted. Since then TB cases have continued to rise. Ten million individuals are infected in the U.S.A., with approximately 26000 new cases of active disease each year (National Jewish Medical and Research Center, 1994).

Individuals infected with Human Immunodeficiency Virus (HIV) are very susceptible to tuberculosis and often develop this disease before other manifestations of AIDS become apparent (Grange and Davey, 1990). Control of the TB epidemic linked with HIV infection will depend largely on the adequate treatment of TB, and possibly of effective chemoprophylaxis, not just for HIV-infected persons but for communities as well (WHO/IUATLD, 1989).

TB therapy has been revolutionized and the present treatment regimes for TB are based on multidrug therapy with usually 3 or 4 antituberculosis drugs. However, the problem of multidrug resistant tubercle bacilli is emerging for various drugs such as isoniazid, ethambutol, rifampicin and streptomycin, for example (Girling, 1989; Grange and Davey, 1990). Drug-resistant TB is very difficult to treat requiring greater numbers and varieties of medications for a longer period of treatment. The need for new antituberculosis agents is urgent due to the increasing resistance of mycobacteria to these classic antituberculosis drugs. A recent WHO report states that, globally, 2% of all cases of tuberculosis are multidrug resistant - by definition, resistance to rifampicin plus isoniazid (plus/minus other resistances). Such cases can be treated in the USA and other high resource regions but at a great cost (> US$ 250,000 per case!) and using very long courses of rather toxic drugs, thereby raising serious problems of compliance (WHO, 1997). South Africa is witnessing an explosion in the number of cases of drug-resistant tuberculosis. In some parts of South Africa, 1 in 10 cases of TB is resistant to treatment (New Scientist, March 1997). It is essential to have new antituberculosis agents, preferably those that can readily and simply be produced from some local source.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a naphthoquinone derivative of Formula 1:

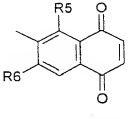


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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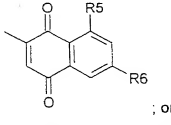

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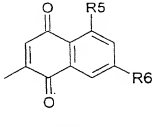
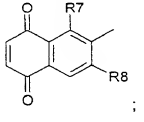


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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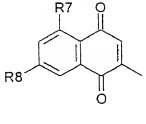

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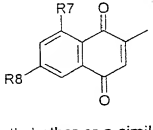


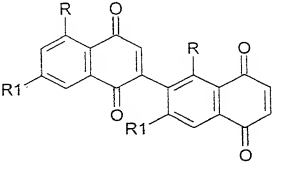
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof, for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

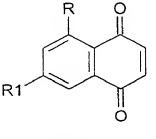
According to a second aspect of the invention there is provided the use of a naphthoquinone derivative having the Formula 1 as set out above in the manufacture of a medicament for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

According to a third aspect of the invention there is provided a method of treating and/or controlling tuberculosis caused by *Mycobacterium tuberculosis* comprising administering to a patient in need thereof an effective amount of a naphthoquinone derivative having the Formula 1 as set out above.

The naphthoquinone derivative of Formula 1 is typically a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 above.

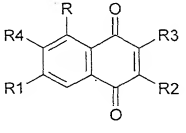
R in the compound of Formula 1a or 1b is preferably an OH group.

R1 in the compound of Formula 1a or 1b is preferably a CH_3 group.

In particular, the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone).

DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed at the use of naphthoquinone derivatives in the treatment and/or control of tuberculosis caused by *Mycobacterium tuberculosis*. In particular, naphthoquinone derivatives of the general Formula 1

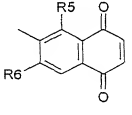


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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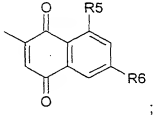

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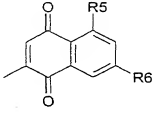
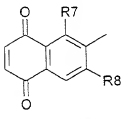


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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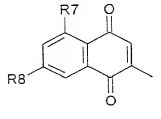

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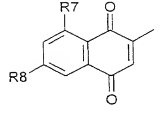
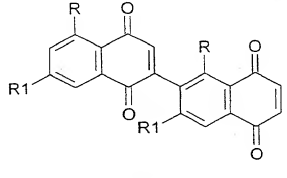


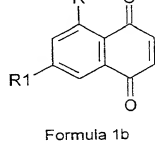
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

have been found to be effective against *Mycobacterium tuberculosis*.

Particular naphthoquinone derivatives of Formula 1a and 1b have been found to be particularly effective:



Formula 1a



Formula 1b

In particular diospyrin and methyljuglone, naphthoquinone derivatives of Formula 1a and Formula 1b, respectively, in which R is OH and R1 is a methyl group, have been found to inhibit several antibiotic resistant as well as antibiotic susceptible strains of *Mycobacterium tuberculosis*. Although diospyrin and methyljuglone are particularly preferred, naphthoquinone derivatives of Formula 1a and 1b in which R is a methyl ether, ethyl ether or similar ether and R1 is an ethyl or similar aliphatic hydrocarbon derivative are also provided.

An extensive research program was undertaken in order to identify anti-tuberculosis agents that can readily and simply be produced from local resources.

Twenty South African medicinal plants used to treat pulmonary diseases were screened for activity against drug-resistant and sensitive strains of *M. tuberculosis*. A preliminary screening of acetone and water plant extracts, against a drug-sensitive strain of *M. tuberculosis*; H37Rv, was carried out by the agar plate method. Fourteen of the 20 acetone extracts showed inhibitory activity at a concentration of 0.5 mg/ml against this strain. Acetone as well as water extracts of *Cryptocarya latifolia*, *Euclea natalensis*, *Helichrysum melanacme*, *Nidorella anomala* and *Thymus vulgaris* inhibited the growth of *M. tuberculosis*. Given the activity of 14 acetone extracts at 0.5 mg/ml against the drug-sensitive strain by the agar plate method a further study was carried out employing the rapid radiometric method to confirm the inhibitory activity. These active acetone extracts were screened against the H37Rv strain as well as a strain resistant to the drugs, isoniazid and rifampicin. The minimal inhibitory concentration of *Croton pseudopulchellus*, *Ekebergia capensis*, *Euclea natalensis*, *Nidorella anomala* and *Polygala myrtifolia* was 0.1 mg/ml against the H37Rv strain by the radiometric method. Extracts of *Chenopodium ambrosioides*, *Ekebergia capensis*, *Euclea natalensis*, *Helichrysum melanacme*, *Nidorella anomala* and *Polygala myrtifolia* were

active against the resistant strain at 0.1 mg/ml. Eight plants showed activity against both the strains at a concentration of 1.0 mg/ml.

The following procedure was developed by the applicant for the isolation of diospyrin and methyljuglone from *E. natalensis* and other species in this genus, as well as any other plants that may synthesise diospyrin or methyljuglone or other quinone derivatives.

1. **Identification of plant species**

   Roots and the aerial plant parts of *E. natalensis* were collected near Durban and identified at the HGWJ Schweickerdt Herbarium of the University of Pretoria and also at the herbarium of the National Botanical Institute, Pretoria.

2. **Extraction**

   Dried roots of *E. natalensis* were ground to a powdery form with a dry mill and extracted over 48 hours with acetone. The extract was filtered and concentrated to dryness at reduced pressure on a rotary evaporator.

3. **Thin layer chromatography**

   A direct antibacterial bioassay (Dilika & Meyer 1996) on TLC-plates was employed to speedup the activity guided isolation of the antituberculosis compounds. *M. tuberculosis* cannot be tested in this way because of its very slow growth rate. The direct antibacterial bioassays of the acetone extract were done on TLC plates (Merck) developed with chloroform-hexane (1:1). After development, the TLC plates were dried and sprayed with a 24 hr old *Staphylococcus aureus* culture in nutrient broth. After 24 hr incubation, the plates were sprayed with an aqueous solution of 2mg/ml p-iodonitrotetrazolium violet to visualise the bacterial cells. The plates were then reincubated at 37°C for 2-3 hours.

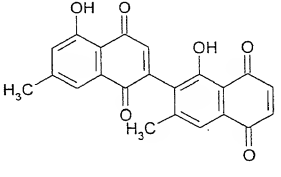
Two zones of bacterial growth inhibition could be seen on TLC plates sprayed with *S. aureus*. Activity was more pronounced in the R_f 0.30 zone (chloroform-hexane (1:1)) than in the R_f 0.54 zone.

4. **Column chromatography**

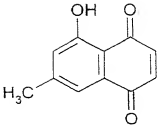
The crude extract of the plant was dried, its mass determined and resuspended in chloroform. Column chromatography was performed on silica gel 60 using chloroform as eluent. The antibacterial fractions collected were then subjected to a Sephadex LH-20 column chromatography using ethanol as eluent. The fractions collected were again tested for antibacterial activity on TLC to detect the fractions containing the active compounds of R_f 0.30 and R_f 0.54.

5. **High performance liquid chromatography**

The compounds were further purified by HPLC utilising an analytical Phenomenex reverse phase 250x4.60 mm column, at a flow rate of 1.0 ml/min, oven temp. 40°C and a wavelength of 206nm. An ethanol-water (50:50) solution was employed as mobile phase. The pure compounds were once again subjected to a Sephadex LH-20 column chromatography and proved to be pure. The chemical structures were confirmed by ^1H and ^{13}C nmr and ms to be:



Diospyrin (5,5' dihydroxy 7,7' binaphthoquinone); $C_{22}H_{14}O_6$. Molecular weight: 374.35



7-methyljuglone (5-hydroxy-7-methyl-1,4-naphtoquinone); $C_{11}H_8O_3$
Molecular weight: 188.19

The effect of diospyrin and methyljuglone on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method are set out in Table 1 and Table 2.

TABLE 1

Effect of diospyrin on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method.

Mycobacterium tuberculosis strains	MIC (mg/ml)	ΔGI[a] values of plant extracts (mg/ml)	ΔGI values of the control vial (mg/ml)
H37 sensitive strain	0.1	-1 ± 1.41	20 ± 4.24
2 drug resistant strain (res. to Isoniazid and rifampicin).	0.1	3.5 ± 0.70	25 ± 7.07
3 drug resistant strain (res. to streptomycin, isoniazid and ethambutol),	0.1	4 ± 2.12	29 ± 1.41

4 drug resistant strain (res. to streptomycin, isoniazid, rifampicin and ethambutol).	0.1	5 ± 2.82	25 ± 2.82
5 drug resistant strain.(res to isoniazid, streptomycin, rifampicin, thiacetazone and cyclocerine).	0.1	10 ± 1.41	22.5 ± 3.53
6 drug resistant strain (res. to isoniazid, rifampicin, ethionamide, terizidone, thiacetazone and ofloxacin).	0.1	9 ± 2.82	30 ± 1.0
7 drug resistant strain.(res to isoniazid, streptomycin, ethambutol, kanamycin, rifampicin, and ethionamide)	0.1	13.5 ±3.2	28 ± 3.1

[a] ΔGI values are means ± s.d.

TABLE 2

Effect of 7-methyljuglone as a single agent and in combination with diospyrin on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method.

Mycobacterium tuberculosis strains	Lab reference no.	Compound(s)	MIC[a] (μg/ml)	ΔGI[b] values of plant extracts	ΔGI values of the control vial
H37Rv sensitive strain	ATCC27294	7-methyljuglone	50	0 ± 1	15 ± 3.78
Two drug (isoniazid and rifampicin) resistant strain	CCKO28469V	7-methyljuglone	50	0 ± 0	30 ± 4.94

H37Rv sensitive strain	ATCC27294	Diospyrin + 7-methyljuglone	10	3 ± 1	15 ± 3.78
Two drug (Isoniazid and rifampicin resistant strain)	CCKO28469V	Diospyrin + 7-methyljuglone	10	3.33 ± 3.05	30 ± 4.94

[a]Minimal inhibitory concentration

[b]ΔGI values are means ± s.d.

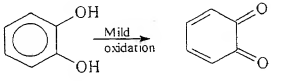
The results show that diospyrin and methyljuglone control the *Mycobacterium tuberculosis* bacterium effectively. Oral administration of diospyrin or methyljuglone in an appropriate pharmaceutical composition with suitable diluents and carriers will typically be used to treat or control tuberculosis. This will be by way of tablet, liquid or similar oral dosage form, as diospyrin and methyljuglone are readily absorbed intestinally.

However, it is believed that diospyrin or methyljuglone administered intravenously or intramuscularly will also be absorbed effectively through blood vessels and the blood stream of a patient. Transdermal administration, via a plaster or similar transdermal administration vehicle, is also a possibility.

A combination treatment of diospyrin and methyljuglone, which may be more effective than singular treatments of the two naphthoquinones, is also envisaged.

The applicant believes that it may be possible to increase the concentration of diospyrin, methyljuglone and other quinones in *E. natalensis* or similar species by phytoalexic stimulation or by the biotechnological manipulation of tissue cultures and/or intact plants.

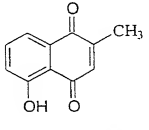
Quinones are generally synthesised from catechol (1,2-quinones) or hydroquinone (1,4-quinones) by mild oxidation.



Catechol

Hydroquinone

As far as the applicant has been able to establish, diospyrin has been synthesised once in a laboratory (Yoshida, M and Mori, K. 2000. European Journal of Organic Chemistry pages 1313 – 1317). However, similar binapthoquinones can also be synthesised by the reaction of plumbagin (94mg in methanol, 10ml) and its hydroquinone (190mg in methanol, 14ml), buffered in phosphate to pH 6.8 at 30°C. (Sankaram et al. 1975; Kumari et al. 1982).

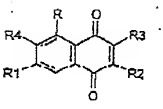


Plumbagin

It is believed that diospyrin, methyljuglone and related naphthoquinone derivatives are viable alternatives to conventional drugs in the treatment and control of tuberculosis in humans.

CLAIMS

1. The use of a naphthoquinone derivative having the Formula 1:

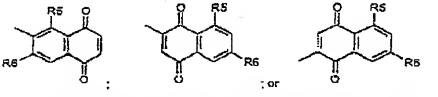


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

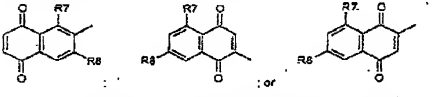
R2 and R3 each independently represent hydrogen or a group selected from:



; or

wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



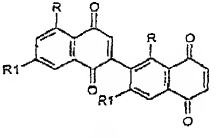
; or

wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

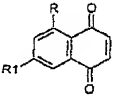
AMENDED SHEET

or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

2. The use according to claim 1 wherein the naphthoquinone derivative of Formula 1 is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 in claim 1.

3. The use according to claim 2 wherein R is an OH group.

4. The use according to claim 2 or claim 3 wherein R1 is a CH_3 group.

5. The use according to claim 1 wherein the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

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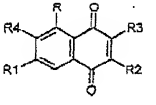
6. A method of treating and/or controlling tuberculosis caused by *Mycobacterium tuberculosis* comprising administering to a patient in need thereof an effective amount of a naphthoquinone derivative having the Formula 1:

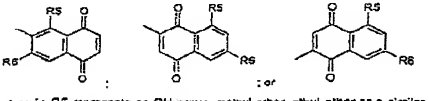


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

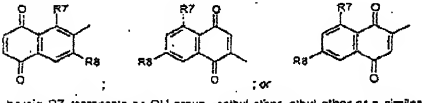
R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:

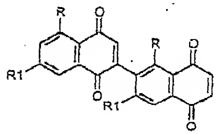


wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

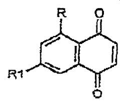
AMENDED SHEET

or pharmaceutically acceptable salts thereof,

7. A method according to claim 6 wherein the naphthoquinone derivative of Formula 1 is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 in claim 11.

8. A method according to claim 7 wherein R is an OH group.

9. A method according to claim 7 or claim 8 wherein R1 is a CH_3 group.

10. A method according to claim 6 wherein the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7'.binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

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11. A method according to claim 6 wherein the naphthoquinone derivative of Formula 1 is administered orally, intravenously, intramuscularly or transdermally.

ABSTRACT

Naphthoquinone derivatives of Formula (1): wherein R, represents an OH group, methyl ether, ethyl ether or a similar ether, R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative: R2 and R3 each independently represent hydrogen or a group selected from: (A), (B), or (C) wherein R5 represents an PH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative: R4 represents hydrogen or a group selected from: (D), (E) or (F) wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative: or pharmaceutically acceptable salts thereof, are useful for the treatment and/or control of a tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

#6

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76) AND POWER OF ATTORNEY

As the below named inventor(s), I/we declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ Application No. 09/926,807, filed on December 21, 2001
  - ☐ as amended on _____ (if applicable);

I/We believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/We have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/We acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including material information which became available between the filing date of the prior application and the National or PCT International filing date of the continuation-in-part application, if applicable; and

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

I/We hereby appoint:

Practitioners at Customer Number 22204 as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

1-00

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Signature:		Date:	
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Signature:		Date:	

☐ Additional inventors are being named on _____ additional form(s) attached hereto.

Burden Hour Statement: This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is used by the public to file (and the PTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This form is estimated to take 1 minute to complete. This time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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